

Bone Marrow and Peripheral Blood Hematopoietic Stem Cell Transplantation: Focus on Autografting

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This review focuses on certain of the principles involved in high-dose chemotherapy and radiation therapy along with autologous hematopoietic stem cell transplantation for the treatment of certain malignancies. In addition, the evidence, wherever possible based on randomized data, for the application of this approach in certain malignancies is reviewed. The malignancies highlighted include acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin lymphoma, Hodgkin disease, and breast cancer.

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Types of Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT)¹ is undertaken most commonly for indications that include malignant disease with an intrinsically unhealthy host marrow, malignant disease with healthy host marrow, or as replacement therapy for defective cell lineages or functions. Most recently, this modality has been explored as a strategy for reeducating the immune system in several autoimmune diseases and as a platform for generating specific immune responses. Before summarizing aspects of the field, it is important to define certain concepts. The types of HSCT are determined by the "relatedness" of the donor and the source of the stem cell product. The possible degrees of relatedness of the donor are indicated in Table 1. The possible source of hematopoietic stem cells is summarized in Table 2. The various types of transplantation are then arrived at by a combi-

nation of the degree of relatedness and the stem cell product source.

Eradication of malignancy by chemotherapy often is limited by tumor resistance or tumor volume. Increasing the dose of chemoradiation therapy may facilitate overcoming such resistance. Dose intensification frequently is limited by attendant bone marrow or other organ injury. Successful application of allogeneic bone marrow transplantation to the treatment of relapsed or refractory acute leukemia has demonstrated, in part, that dose intensification can produce curative results (1). Another component responsible for the beneficial effects observed with allografting relates to the possibility that donor hematopoietic elements may exhibit the ability to mount a specific immune response against the malignant process. Allogeneic HSCT is, however, complicated by substantial morbidity and mortality related not only to the preparative regimen but also to graft-vs-host disease or complications associated with chronic immunosuppression (2). The significant attendant morbidity and mortality have until recently restricted the age range eligible and performance status required for treatment with this modality. Improvements in supportive care have allowed for some increase in the age threshold provided that physiologic status is adequate (3). Treat-

¹ Nonstandard abbreviations: HSCT, hematopoietic stem cell transplantation; SD, standard-dose therapy; AHSCT, autologous HSCT; HDC, high-dose chemotherapy; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; AML, acute myeloid leukemia; CR, complete remission; IC, intensive chemotherapy; DFS, disease-free survival; OS, overall survival; TRM, treatment-related mortality; CI, confidence interval; ALL, acute lymphoblastic anemia; NHL, non-Hodgkin lymphoma; PFS, progression-free survival; EFS, event-free survival; MOPP, Mustargen-Oncovin-procarbazine-prednisone; EBMT, European Bone Marrow Transplant Registry; TBI, total body irradiation; RR, relapse rate; ASCO, American Society of Clinical Oncology; CALGB, Cancer and Leukemia Group B; STAMPE, Solid Tumor Autologous Marrow Transplant Program; and FEC, 5-fluorouracil, epirubicin, and cyclophosphamide.

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Table 1. "Relatedness" of donor.

- Autologous: self
- Syngeneic: identical twin
- Allogeneic: related
 - Matched at the class I and II loci
 - Mismatched
- Allogeneic: unrelated
 - Matched
 - Mismatched
- Xenogeneic: species

ment failures therefore relate primarily to regimen-related toxicity, complications of graft-vs-host disease or immunosuppression, or on occasion to disease recurrence or relapse.

The recent recognition that nonablative allogeneic transplantation, or the so-called "minitransplant", is feasible and seemingly efficacious may extend allografting to a broader array of patients (4, 5). The fundamental difference between this approach and the traditional allotransplant is that less reliance is placed on the tumoricidal properties of the conditioning regimen and more is placed on the powerfully cytotoxic effect of an allogeneic immune response. Immune suppression rather than myeloablation is the basis for achieving donor hematopoietic engraftment.

The ready availability of an appropriate donor of allogeneic stem cells remains a limitation to its application even in the setting of the leukemias and lymphomas. Because only 35–40% of patients have an HLA-identical sibling, alternative stem cell sources have been the subject of investigation. The use of matched unrelated donors and umbilical cord stem cells continues to expand the options for allogeneic transplantation. Nonetheless, there has been increasing interest over the past two decades in the development of autologous bone marrow and hematopoietic stem cell transplantation for leukemias, lymphomas, myeloma and solid tumors. The general model for autologous transplantation is shown in Fig. 1. Much reliance for efficacy resides with the activity of the induction regimen. Increasingly, new research efforts are aimed at improving outcome by application of strategies aimed at elimination of minimal residual disease after the autograft using non-cross-resistant and frequently distinct approaches. The reasons that autotransplantation might

Autologous Transplantation - General Model

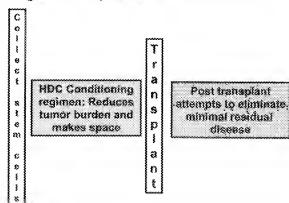


Fig. 1. General model for autologous stem cell transplantation.

Reliance is placed on the tumoricidal properties of the conditioning regimen to maximally debulk the tumor. There is no graft-vs-tumor effect. Attempts at eliminating minimal residual disease rely on non-cross-resistant strategies.

fail are outlined in Fig. 2. Autologous transplantation is a field in rapid evolution and is the major focus of this review.

Autologous HSCT

REQUIREMENTS

The malignancy being treated should be responsive to dose-intensive chemotherapy but not be curable with standard-dose therapy (SDC). Stem cells capable of producing complete trilineage hematopoietic engraftment must also be available. Bone marrow harvest was initially the preferred source of stem cells, but it has been largely replaced by leukapheresed mobilized peripheral blood

Autologous Transplantation - Causes of Failure

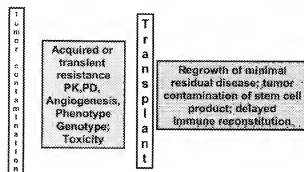


Fig. 2. Outline of the factors that might contribute to treatment failures in autologous transplantation.

Factors include resistance related to cell kinetics, acquired alterations in pharmacokinetics (PK) and pharmacodynamics (PD) of the preparative regimen, effects of standard therapy on angiogenesis, and development of a resistant genotype or phenotype. Outcomes may be adversely affected by TRM. Relapses occur from regrowth of minimal residual disease, and the extent to which delayed immune reconstitution exacerbates this is still unclear. Recurrence may also derive from viable cancer cells introduced with the stem cell product (bypass resistance).

Table 2. Sources of stem cells.

- Marrow
 - Unmobilized
 - Mobilized with chemotherapy and/or growth factors
- Peripheral blood
 - Growth factor mobilized
 - Chemotherapy and growth factor mobilized
- Umbilical cord
- Fetal liver

progenitor cells. It is not yet convincingly established that the stem cell product needs to be completely free of limited numbers of cancer cells. Certain myeloma (6) and the lymphoma (7) data suggest that limited contamination may not preclude successful autologous HSCT (AHST). To reduce such contamination, strategies ("purging") have been explored to remove malignant cells.

HIGH-DOSE CHEMOTHERAPY

The dose-response relationship for many chemotherapeutic agents, such as the alkylators, is steep. Even with chemotherapy-resistant experimental cancers the dose-response relationships are linear-log. Moreover, the dose-response curve does not appear to plateau. This is not the case for all antineoplastic agents. The primary dose limitation for many agents is bone marrow suppression. Certain other drugs have major organ toxicity at or near the myelotoxic dose. The use of high-dose chemotherapy (HDC) exploits differences between the myelotoxic and nonhematopoietic toxicity-defined doses for a given agent provided this difference is also associated with antineoplastic activity. In general terms, the difference between the myelotoxic dose and that producing unacceptable damage to other organs is usually <10-fold (8).

COMBINATION CHEMOTHERAPY

Radiation therapy and chemotherapy have been used in AHST. The frequent finding of drug resistance to any single agent in a cancer cell subpopulation generally mandates the use of multiple drugs, with or without radiation therapy. Agents identified for HDC should have activity against the neoplasm being treated. However, several myelosuppressive agents have not been tested at high doses because of myelosuppression in the absence of stem cell support. Although total body radiation has a role in transplantation for acute leukemias and lymphomas, it is of limited value in solid tumors where doses required for elimination of disease often exceed the tolerable limits of administration. Many agents are not amenable to dose escalation or do not have a linear dose-response effect. Antimetabolites such as 5-fluorouracil and methotrexate plateau in their dose-response after modest dose escalation. Other agents with a steep dose-response effect, such as doxorubicin and the taxanes, produce nonhematopoietic toxicities that quickly limit further dose escalation. Cardiac, mucosal, and epithelial toxicity limit dose escalation for doxorubicin, whereas cutaneous toxicity limits docetaxel and neuropathy restricts intensification of paclitaxel. It is unlikely that such compounds will play a major role in HDC regimens, although synergy with other active agents could provide a role in high-dose programs.

DISEASE VOLUME AT TRANSPLANTATION

Tumor kinetic modeling has provided some guide to therapeutic regimens using AHST. The Goldie-Coldman

(9) hypothesis indicates that spontaneous development of resistance occurs early in cancer evolution and that consequently treatment in early stage of disease is desirable. Whether HDC will produce sufficient increase in therapeutic effect to overcome resistance, particularly in combination regimens, is at present uncertain for most tumors. The Norton-Simon model would predict that HDC after cytoreduction would represent optimal scheduling for dose intensification (10-12). Formal testing of these hypotheses is the subject of current studies. Although initial bulk reduction of tumor with SDC before HDC makes intuitive sense, there remains the distinct possibility that sequelae of the induction may contribute to acquired resistance and to some extent mitigate the efficacy of HDC.

PATIENT SELECTION

Age is less of a barrier to AHST than allogeneic transplantation because of the absence of graft-vs-host disease. Although a rare event, successful autografting has been performed into the eighth decade. Concurrent illness may increase the morbidity of AHST for patients of advanced age. Initial patient performance status is a major predictor of toxicity in AHST. Patients who have failed multiple prior therapies may not be good candidates for HDC because resistant tumor cells may have been selected, increasing the likelihood of failure. It is reasonable in such patients to offer participation in developmental regimens evaluating dose escalation of novel agents and combinations.

Peripheral Blood Stem Cell and Progenitor Cell Collection

The current preferred method for collecting hematopoietic progenitor cells involves leukapheresis to collect peripheral blood mononuclear cells. Circulating numbers of these cells increase during marrow recovery after chemotherapy and after priming with hematopoietic colony-stimulating factors (CSFs) such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF). The best tested approach is mobilization with G-CSF administered subcutaneously at a dose of $10-16 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. This produces adequate mobilization 80-90% of the time. The kinetics of mobilization produce peak progenitor concentrations on days 4-7 after commencing the growth factor. Progenitor yield usually is maximal on the first or second collections and thereafter declines. Conventional mobilization fails in ~10-20% of patients. Patient characteristics, including extensive prior chemotherapy, prior radiation therapy, or extensive cancer burden, may predict poor mobilization. However, in a majority of those failing standard G-CSF mobilization, no obvious cause can be found. For those failing conventional mobilization or requiring larger than usual numbers of stem cells for particular processing, additional mobilization strategies may be used. These generally consist of higher than usual doses of G-CSF, combinations of chemotherapy and G-

CSF, or combinations of growth factors such as G-CSF with GM-CSF. The kinetics of mobilization with combined chemotherapy and G-CSF are different from growth factor alone. With chemotherapy such as cytoxan (2 g/m^2) and paclitaxel (175 mg/m^2) with G-CSF at $10 \text{ } \mu\text{g/kg}$ as priming (13), most patients have recovery of counts and an adequate circulating progenitor mass to begin collection by approximately the 10th day after chemotherapy. A major difference from growth factor mobilization is that the peak yield of progenitors is sustained on the subsequent 5–7 days thereby facilitating flexibility in scheduling of apheresis.

In the late 1970s, it was demonstrated that circulating mononuclear cells could produce complete and sustained hematopoietic engraftment in patients with chronic myeloid leukemia after HDC. This has subsequently been demonstrated for most diseases. Recent identification of an early stem cell phenotype (CD34+) has allowed us to define with greater confidence the number of progenitor cells required for hematopoietic reconstitution. Optimization of mobilization regimens has increased the numbers of potentially harvestable progenitor cells present in the peripheral circulation. Progenitor cell quantification in the peripheral blood is beginning to allow us to predict the optimal timing for maximal progenitor cell yields by apheresis (14). Appreciation of the proportionality between volume of apheresis and the number of progenitors collected (15), that progenitor cells are recruitable during apheresis (16), and that large-volume leukapheresis is safe has led to its routine use at the time of maximal circulating progenitor cell number (17). This procedure, which in which in excess of 20 L of autologous blood are processed, reduces the total number of procedures, potentially improves progenitor cell quality, and reduces the total costs associated with apheresis (18). Optimal progenitor yield is best achieved using a measure of the circulating progenitor cell mass rather than the elapsed time from commencement of the mobilization strategy; together with large volume leukapheresis, this approach allows the number of apheresis procedures to be reduced. Enumeration of the number of circulating CD34+ cells has been highly predictive of progenitor cell yield (19). One consequence of the large-volume pheresis is that patients receive substantial amounts of citrate as part of the anticoagulation required to maintain flow through the vascular access and the pheresis device. This may lead to hypocalcemia. To limit or prevent this, enteral and parenteral administration of calcium is may be required. The amount needed is a function of the amount of citrate actually administered. The biochemistry laboratory therefore plays a key role in monitoring vital electrolytes during this procedure.

Mononuclear cells collected in this fashion are concentrated and cryopreserved. Cryopreservation requires addition of a cellular cryoprotectant, and the one most commonly used is dimethyl sulfoxide. At the time of thawing and stem cell re-infusion, the dimethyl sulfoxide

along with the product's cold temperature may produce an unpleasant taste and odor, nausea, vomiting, chest discomfort, blood pressure, and cardiac rate and rhythm alterations. Certain centers routinely wash the thawed product to minimize side effects and limit discomfort attributable to the dimethyl sulfoxide.

Adequate hematopoietic reconstitution correlates with the number of progenitor cells measured in the colony forming unit-granulocyte macrophage (CFU-GM) assay. Enumeration of CD34+ progenitors is of equal value in identifying the adequacy of the stem cell product but at a fraction of the cost and labor. The minimal threshold for an adequate stem cell product appears to be $>2.5 \times 10^6$ CD34+ progenitors/kg of patient weight. The ideal target should be on the order of double this to ensure rapid platelet recovery. Although it is claimed that peripheral blood progenitor collections have fewer contaminating malignant cells, even in patients with acute myeloid leukemia (AML), chronic myelogenous leukemia, lymphoma, or solid tumors in which bone marrow contamination is evident, recent data suggest that peripheral blood progenitor collections do contain tumor cells.

Specific Diseases in Which AH SCT Has Been Evaluated

In this section, we summarize currently available data relating to the efficacy of AH SCT in certain of the more commonly applied disease settings. Where available, the pertinent randomized study data are highlighted.

AML

Randomized comparative data in first complete remission (CR) studies as well as studies in which high-dose consolidation control arms without AH SCT were used have recently been completed and communicated. Indeed, in the past 5 years large randomized trials comprising >2500 people have compared the use of AH SCT to intensive chemotherapy (IC) as consolidation for patients with AML in their first CR (20–24). All of these studies have exhibited feasibility limitations, with ~30% of those randomized to autotransplant arms not completing assigned treatment. With this rate of protocol deviation, the power of the study frequently is compromised in the customary intention-to-treat analysis. Analysis based on actual treatment received frequently is more positive. The results of these studies are summarized in Table 3.

A metaanalysis of these data establishes significant improvement in disease-free survival (DFS) for AH SCT over IC. Overall survival (OS) improvement does not achieve statistical significance, with an odds ratio of death for AH SCT compared with IC of 0.82 [95% confidence interval (CI) = 0.61–1.1; $P = 0.19$]. Efficacy of salvage treatment and treatment-related mortality (TRM) on the AH SCT arm may contribute to this. Up to 20% of those relapsing on the IC arm received an AH SCT. This is a common problem in interpretation of all randomized transplantation studies.

Table 3. Summary of recently completed randomized studies of allogeneic transplantation, AHSCT, and intensive chemotherapy consolidation in first complete response in AML.

Study	IC	Purging	% completing assigned Rx, ^a Allo/Auto/IC	4-year DFS, %: Allo/Auto/IC	4-year OS, %: Allo/Auto/IC	TRM, %: Allo/Auto/IC
French (20)	HD AraC + IDR or RBZ	—	83/85/90 ^b	50/44/40	55/50/54	22/7/3
MRC 10 ^c (21)	No further treatment	—	—/66/97	—/54/34	—/57/45	—/12/4
SWOG/ECOG/CALGB (22)	HD AraC	+	91/54/81	43/35/35	46/52/43	25/14/3
EORTC/GIMEMA (23)	HD AraC + Dauno	—	86/74/83	55/48/30	59/56/46	17/9/7
POG (24)	6 courses of Dauno AraC, VP16	+	87/62/97	52/38/36	51/37/42	5/11/3

^a Rx, treatment; Allo, allogeneic transplantation; Auto, AHSCT; HD, high dose; AraC, cytosine arabinoside; IDR, idarubicin; RBZ, rubidazole; Dauno, daunomycin; VP16, etoposide.

^b Forty percent of patients lost before randomization between AHSCT and IC.

^c Control arm received only induction therapy.

ACUTE LYMPHOBLASTIC LEUKEMIA

Results of AHSCT in acute lymphoblastic leukemia (ALL) have been less impressive. In a comparison of autografting to allografting in 91 patients with ALL in the first through fourth remission, 20% of autografted and 27% of allografted patients became long-term disease-free survivors (25). Nonrandomized analyses of substantial data sets (26–28) failed to reveal any advantage for AHSCT over chemotherapy in ALL. These data are summarized in Table 4. AHSCT and chemotherapy provide similar DFS and OS benefits for patients with ALL in their second or subsequent CR. No maintenance chemotherapy usually is given with AHSCT.

An apparent advantage for allografting over AHSCT suggests possible graft-vs-leukemic effects. Initial analysis of 47 patients suggested that the probability of relapse was 9% for patients receiving an allogeneic bone marrow transplant and 52% for patients receiving AHSCT (29). Given the apparent lack of an effect of donor lymphocyte infusions, the magnitude of a graft-vs-leukemic effect in ALL appears limited. Donor lymphocyte infusion is the process whereby donor lymphocytes are infused to a recipient after relapse post allogeneic transplantation in an attempt to produce a graft-vs-leukemic effect and thereby eliminate malignant cells. Nonrandomized studies have compared AHSCT to allogeneic transplant in

ALL. Patients with an HLA-matched sibling donor received an allograft, whereas those lacking a donor underwent AHSCT. There appeared to be a trend to improved DFS and OS in the allogeneic arms (26, 30, 31), particularly when the patient was treated after first CR (26, 27, 29, 32). These data are summarized in Table 5. This trend was significant in two of three studies (29, 33) in those patients treated in first CR.

NON-HODGKIN LYMPHOMA

The outcome of AHSCT in non-Hodgkin lymphoma (NHL) is determined by grade and extent of disease and resistance to previous chemotherapy. In advanced-stage intermediate and high-grade lymphoma, 3-year progression-free survival (PFS) ranges from 20% to 60%, reflecting small study numbers and selection effects. In general, results are superior for patients with smaller volume and induction chemotherapy-sensitive disease (34).

The Parma study (35) has established AHSCT as standard treatment in relapsed chemotherapy-sensitive NHL. Two hundred fifteen patients in relapse were randomized to SDC plus radiation or HDC with AHSCT plus radiotherapy. After 5 years of follow-up, AHSCT had a significantly better event-free survival (EFS) and OS compared with the SDC group (46% vs 12%; $P = 0.001$; and 53% vs 32%; $P = 0.04$).

Table 4. Nonrandomized comparisons between AHSCT and standard chemotherapy in ALL.^a

Study	No. patients Auto/Ctx ^b	Patient details	Purging	TRM, %: Auto/Ctx	RR, %: Auto/Ctx	EFS, %: Auto/Ctx (years)	OS, %: Auto/Ctx (years)
UKALL X, 1998 (26)	489 61/261	Relapsed 2nd CR	+	5/5	64/65	31/30	34/40
Berlin, 1995 (27)	104 52/52	Pediatrics 2nd CR	40% purged	2/4	62/65	32/26 (9)	
French group, 1993 (28)	191 95/96	Adults 1st CR	+	4/4	61/57	39/32 (3)	49/42 (3)

^a All are retrospective studies with consequent limitations in interpretation of data.

^b Auto, AHSCT; Ctx, chemotherapy.

Table 5. Nonrandomized comparisons between autografting and allografting for ALL.

Study	No. patients Auto/Allo	Patient details	Purged product	TRM: Auto/Allo, %	RR: Auto/Allo, %	DFS: Auto/Allo, % (years)	OS: Auto/Allo, % (years)
U of Minnesota (25)	91 45/46	Any remission	+	6/33	69/33	20/27 (4)	23/31 (4)
AIEOP (30)	66 35/30	Any remission/relapse	+	8/17	47/30	50/56 (2)	58/68 (2)
Boston (31)	75 57/17	Pediatric 2nd or subsequent CR	+	7/18	47/31	47/53 (3)	
UKALL X (26)	489 61/110	Relapsed/2nd CR	+	5/17	64/39	31/44 (5)	34/48 (5)
French Coop group (29)	47 22/25	HR,* 1st CR	+	9/20	52/9	40/71 (2)	62/71 (2)
French group (28)	211 95/116	Adults; 1st CR	+	4/15	57/28	39/44 (3)	47/56 (3)
France (33)	120 77/43	1st CR/early relapse	—	2/12	70/17	30/68 (3)	30/71 (3)

* HR, high risk.

Three of five randomized controlled trials show positive value for AHSCT as initial treatment for high-risk NHL. The GELA (LNH 87-2) study (36), the Milan study (37), and the study by Santini et al. (38) reported that HDC with AHSCT improves DFS, EFS, and OS (See Table 6). Two other studies, one from the GELA group (LNH93-3) (39) and the other from the German Lymphoma Group (40), found SDC better than AHSCT with respect to EFS and OS in this high-risk group. These data are summarized in Table 6. Compliance with AHSCT as a treatment strategy was a problem in all studies, with 26–29% of those randomized to transplant not able to receive this treatment, usually because of early relapse or patient refusal.

Slow response to induction chemotherapy was thought to be a poor prognostic factor for NHL. Two small trials were discordant, with one reporting a trend to improved survival with AHSCT and a second supporting SDC (39, 40). The role of AHSCT in this setting remains to be established. For resistant disease, the Autologous Blood and Marrow Transplant Registry data indicate that this poor prognosis group derive some benefit from AHSCT with the probability of PFS and OS at 3 years being on the order of 32% and 40%. Canellos et al. (41), in a survey of published reports, showed only 16 of 112 long-term disease-free survivors when AHSCT was used for refrac-

tory relapse of lymphoma, as opposed to 33 of 53 patients transplanted in second or subsequent remission or in first partial remission.

A series of phase II studies in follicular center cell NHL have shown promising results. The long survival of patients with follicular lymphoma demands protracted follow-up, as shown in data from the Dana Farber Institute (42) that identify prolonged survival after AHSCT compared with historical examples. Patients with chemotherapy-sensitive disease had a 12-year survival from diagnosis of 70%. Eighty-three percent remained in molecular remission at 6 years. If the bone marrow was negative by PCR for t(14;18), a characteristic follicular center cell translocation, OS was significantly better.

HODGKIN DISEASE

HDC with AHSCT can provide 45% OS at 6 years in patients failing a regimen similar to the Mustargen-Oncovin-procarbazine-prednisone (MOPP) regimen and Adriamycin-containing therapy for relapsed Hodgkin disease (43). Outcome is inversely proportional to performance status before HDC, the amount of prior chemotherapy, and tumor volume, and is negatively impacted by the disease recurrence within a previous radiation field. Any of these features reduce the probability of long-term survival. Similar treatment results have been

Table 6. Randomized studies of AHSCT vs SDC in patients with high-risk NHL.

Study	DFS		OS	
	AHSCT/SDC, % (years)	P	AHSCT/SDC, % (years)	P
GELA 87-2 (36)	59/39 (5)	0.01	65/52 (5)	0.06
Milan (37)	76/49 (4.5)	0.004	81/55 (4.5)	0.09
Santini et al. (38)	87/48 (3)	0.008		NS ^a
GELA 93-3 (39)	47/63 (3)	0.003	47/63 (3)	0.003
German Lymphoma Group (40)	NR		58/70 (2)	NR

^a NS, difference not significant; NR, not reported.

reported for AHST and allogeneic transplantation for Hodgkin diseases (44), indicating limited graft-vs-lymphoma effect. Given the morbidity and mortality associated with allogeneic transplantation, AHST represents the preferable approach for relapsed Hodgkin disease.

The role of AHST is established for patients who do not obtain a CR with primary SDC. Median survival in this group is 16 months with a very poor (0%) 8-year survival rate with standard therapy (45). One small, randomized control trial compared AHST with SDC in Hodgkin disease (46). This study compared SDC salvage with AHST in 40 patients, one-half of whom never reached CR. The remainder of the patients had relapsed in the first year after initial treatment. A significant improvement in EFS for AHST over SDC (53% vs 10%; $P = 0.025$) at 5 years was observed along with a trend toward improvement in OS (46). The Autologous Blood and Marrow Transplant Registry data on 122 patients who failed to reach CR after one or more standard regimens and then were treated with AHST revealed probabilities of PFS and OS at 3 years of 38% and 50%, respectively (46). The European Registry reported on 290 patients with primary refractory disease (no response or progression on primary therapy) treated with AHST, showing PFS and OS of 30% and 34%, respectively, at 5 years (47). In a reported series of 46 patients who were primary refractory, 33% achieved a 5-year PFS with AHST (48). A case-control study compared patients with relapsed disease or progression on primary therapy who were treated with AHST or SDC (49). EFS at 5 years was 52% for AHST and 19% for the standard therapy ($P = 0.01$), and OS was 44% and 38%, respectively ($P = 0.32$).

If patients do achieve a CR with standard chemotherapy, the optimal timing of AHST in HDC has yet to be defined. AHST as consolidation in high-risk patients is supported by nonrandomized and retrospective data. Patients refusing transplant were compared in terms of DFS and OS with those who underwent the treatment modality (50). After 7 years of follow-up, OS for the transplanted group was 77% compared with only 33% for those refusing AHST. The French and European registries indicate an advantage with respect to DFS when AHST consolidation is used in high-risk patients. The French registry reported an OS of 83% and EFS 73% at 7 years (51–53).

AHST in first relapse has been shown superior to SDC. A recent randomized study, comparing standard-dose and high-dose bischloroethylnitrosourea-etoposide-arabinosylcytosine-melphalan with AHST, found a significant improvement in DFS with HDC in chemotherapy-sensitive first relapse. Another study reported PFS of 48–85% at 2.3 years with AHST for patients in first relapse (54). SDC produced a DFS of 15–51% (55,56). Duration of remission was found to be a significant prognostic factor both in the AHST and standard dose setting. Indeed, the advantage of AHST over SDC in a matched-pair analysis was seen primarily in the high-risk

patients who had relapsed in the first year (PFS, 56% vs 19%; $P < 0.01173$). No benefit to AHST was found in those with an initial remission of >12 months duration. However, European Bone Marrow Transplant Registry (EBMTR) data indicate that all patients past first relapse benefited equally from AHST, regardless of the duration of remission (57).

MULTIPLE MYELOMA

Chronological and biological circumstances prevent many myeloma sufferers from being considered for HDC and AHST. There is a steep dose-response effect for alkylating agents in patients with disease refractory to SDC. Melphalan appears preferable to cyclophosphamide in small, uncontrolled observations (58). Several large pilot studies were initially reported in which high-dose melphalan or thiotepa, with or without total body irradiation (TBI) were used in previously treated patients. CR was observed in 25–50% of patients.

A randomized study from the French Intergroup for Myeloma established AHST as standard of care for multiple myeloma (59). Patients randomized to SDC at diagnosis had a 6-year EFS and OS of 15% and 21%, respectively, compared with the AHST arm with 24% and 43%, respectively ($P < 0.01$ and < 0.03). The timing of the transplant is less well established. Minimal exposure to marrow-toxic alkylating agents and nitrosoureas is preferred. A current Intergroup trial addressing the question of early vs delayed transplant has been completed, and accrual and results are eagerly awaited.

The French randomized study excluded those older than 65 years of age. This age criterion has been challenged. Age was found not to be a prognostic factor for EFS or OS when patients ≥ 65 years of age were compared with younger patients (60). Other reports have positive results with patients up to the age of 70.

Outcomes after "total therapy" with tandem transplants have been reported by the Arkansas group with a projected 5-year EFS and OS of 36% and 61%, respectively (61). The French Intergroup for Myeloma performed a randomized control trial contrasting single with tandem transplants. Early results revealed little difference, with 2-year probabilities of EFS and OS in the single AHST arm of 54% and 71%, respectively, with the double transplant producing similar results at 57% and 67% (62). A review of EBMTR data failed to reveal improvement in survival with tandem transplants over single transplants (63, 64).

Purging the bone marrow or peripheral blood stem cells has not been shown to be a predictive factor in survival. The majority of published studies do not use purged marrow. The number of multiple myeloma cells in the collected product increases after 3 days of collection. Abnormal cytogenetics have been demonstrated to be a major predictor of an adverse outcome.

The data from the EBMTR (66) indicate that non-TBI conditioning produces improvement in survival. This has

been confirmed in studies that found that adding TBI to HDC did not significantly increase the response rate (67) and that TBI did not improve relapse rate (RR), PFS, or OS. In tandem transplantation, melphalan alone had better TRM, EFS, and OS than the TBI containing group when used in the second transplant treatment regimen. (TRM, 0% vs 8%; EFS, 44 vs 16 months; OS, 65 vs 31 months) (67). AHSTCT for multiple myeloma can be a cost-effective procedure with only 21% of patients requiring admission to hospital (68).

BREAST CANCER

The appropriate role for HDC and AHSTCT for breast cancer remains unresolved. Media reporting surrounding the 1999 American Society of Clinical Oncology (ASCO) meeting suggested conclusions disparaging of HDC and AHSTCT. Because discussion of these preliminary data before the meeting was not permitted, media reports were unchallenged and unencumbered with critical data evaluation and fact. The inappropriate nature of this intense public debate over preliminary abstract data has been highlighted by subsequent events. One reportedly negative analysis on critical reevaluation is strikingly positive, one randomized study reported as negative has on review many apparent design and conduct flaws, and a third study reported as positive on audit has raised questions of scientific misconduct. This has led to confusion and anxiety for patients and their doctors. Fortunately, two randomized studies reported at the 2000 ASCO meeting that are strikingly positive in favor of HDC and HSCT have begun to help clarify the situation. One fact is clear: SDC for breast cancer, even with the advent of new biologics (herceptin) and the addition of taxanes, is poor, with most metastatic disease patients succumbing in 5 years and >50% with primary disease dying with disease.

Given the poor outcomes in high-risk primary disease with SDC, HDC and AHSTCT have been explored for potential therapeutic improvement. Much impetus derived from a study of 85 women within Cancer and Leukemia Group B (CALGB) involving the use of high-dose cyclophosphamide, cisplatin, and carmustine [Solid Tumor Autologous Marrow Transplant Program (STAMP) I regimen] as consolidation after an intensive regimen of cyclophosphamide, doxorubicin, and 5-fluorouracil in CALGB 8782 (69,70). That study demonstrated EFS in excess of 60% at a median follow-up of 7 years. SDC alone, over a period of 17 years within the CALGB, produced markedly inferior outcomes. The initial favorable HDC data have been recapitulated in several phase II studies and a large body of registry data. The results of three randomized studies of HDC and SCT in the treatment of women with 10 or more positive nodes were presented at the ASCO 1999 meeting, and an additional study was presented at the ASCO 2000 meeting. Summary data as well as two previously reported underpowered randomized studies are presented in Table 7.

In CALGB 9082, 785 patients were equally randomized per protocol to consolidation with high- or intermediate-dose cyclophosphamide, cisplatin, and carmustine (71). Fewer relapses occurred in patients who received HDC compared with non-HDC throughout the first 3 years of follow-up. There were 126 relapses on the non-HDC arm and 85 on the HDC arm, reflecting a reduction in relapse frequency from 32.2% (95% CI, 27.6–36.9%) to 21.6% (95% CI, 17.5–25.6%). This represented a 34% reduction in relapse frequency. There was no overlap between the CIs. The current follow-up on the whole patient population is inadequate for definitive statistical analysis. Analysis of the first 341 patients, the original study design sample, and with a median follow-up of 5.1

Table 7. Randomized studies of HDC in primary breast cancer.

PI: ^a Study, (HDC regimen)	Patient numbers	Median follow-up, years	Results of study at presentation
Peters: CALGB 9082/SWOG 9114/NCIC MA13 (STAMP I) (71)	874	3.5	34% decrease in relapses; short follow-up EFS and OS same; toxicity center- and age-dependent; 7% transplant mortality
Bezwdia: South African (CNV) (72)	154	5	Statistically and clinically significant improvement in DFS and OS; no transplant mortality. Audit has raised issues of scientific misconduct
Berg: Scandinavian Study Group (STAMP V) (73)	525	1.7	Very short follow-up; 133 relapses OS same; total dose on non-transplant arm markedly higher; no transplant mortality; 7 cases MDS/AML on control arm
Rodenhuis: Dutch Study Group (STAMP V) (74)	81	4.5	No difference in DFS or OS; significant design flaws; underpowered study
Hortobagyi: MDA (CEP) (75)	78	4	No difference in DFS or OS; underpowered, study closed early—slow accrual
Rodenhuis NAST (modified STAMP V) (76)	885		15% reduction in 3-year PFS ($P = 0.009$) and 10% reduction in OS ($P = 0.039$) for the first 284 patients analyzed per protocol; for entire group trends the same but follow-up too short; 1% TRM

^a PI, principal investigator; CNV, cyclophosphamide-mitoxantrone-VP16; MDS, myelodysplasia; CEP, cyclophosphamide, etoposide, and Platinol.

years showed an absolute difference in EFS in favor of HDC of 12% at 36 months, 8% at 5 years, and 25% at the lead follow-up of 84 months. Transplant TRM was 7%, 5.9% at the largest accruing center, 7.9% at the second, and >10% at the other centers (71). These data suggest that HDC appears more effective in controlling recurrence of breast cancer. HDC was associated with significant treatment-related toxicity, which was not completely ameliorated by the use of stem cell transplant and may have been influenced by patient age and experience of the center. The trial design allowed patients who relapsed after non-HDC to proceed on to transplant (71). Consequently, OS between the arms was not a primary endpoint.

The second study presented at the 1999 ASCO meeting was performed in South Africa (72). Audit of this study has raised the possibility of scientific misconduct. The third study presented at the ASCO meeting came from Scandinavia (73). Patients were randomized to receive either nine courses of an escalated 5-fluorouracil, epirubicin, and cytoxan (FEC) regimen or two cycles of conventional FEC, followed by a modified FEC, followed again by HDC using cyclophosphamide, thiotepa, and carboplatin (CTCb or STAMP V). Follow-up was very short at <20 months (73). There was no prescreening with computed tomography scans and the other staging methods used in the CALGB and other studies. This may account for high numbers of relapses (133 of 525). As was noted by discussant Dr. Karen Antman, this study uses markedly escalated doses on the SDC arm, making comparison between the two arms problematic. These high "SDC" doses may have contributed to the high rate of acute leukemia and myelodysplastic syndrome observed on the SDC arm.

Two underpowered randomized studies have been presented previously from the Dutch group (74) and from MD Anderson (75). Problems of patient compliance with randomization and the size of the studies limit their ability to provide useful guidance for clinical care. This is emphasized by the subsequent large randomized study from the Dutch group discussed below (76).

Given what we know from the pilot data, the duration of follow-up for the studies from Scandinavia and the US indicates that the OS data might not, at this moment in time, be interpretable. Observations emphasizing the importance of appropriate follow-up have been made in the analysis of the Parma study of relapsed lymphoma. When first presented, there was no statistical difference between SDC and HDC. However, with additional follow-up, statistically significant differences between the two arms developed.

That the place of HDC and AHST in breast cancer is not yet resolved was emphasized at the recent ASCO 2000 meeting. The preliminary analysis of 284 patients entered into an 885 patient phase III study of HDC vs SDC in high-risk primary breast cancer (four or more lymph nodes) by the Netherlands Working Party on Autotrans-

plantation in Solid Tumors (NAST) was presented (76). The HDC was a modified STAMP V regimen in which the dose of thiotepa was reduced and that of carboplatin escalated based on pharmacokinetic data indicating that thiotepa may reduce area under the cytoxan curve, thereby making traditional STAMP V a relatively less effective regimen. The SDC regimen was FEC. For the initial 284-patient cohort analyzed per protocol, there already is a highly statistically significant 15% reduction in relapse-free survival and 10% reduction in OS. It is also important to observe that patients receiving SDC were not able to cross over to HDC at progression.

There now are five available randomized studies in metastatic breast cancer. Two, including the study by Peters and co-workers (the AFM randomized trial) (77,78) and the study from Bezudova et al. (79) from South Africa, have been presented previously at ASCO meetings. Both demonstrated improvement in EFS for patients receiving HDC compared with SDC alone [South African study (79)] or as consolidation after an SDC induction [AFM randomized trial (77,78)]. Two randomized studies of HDC in metastatic disease were presented at the 1999 ASCO meeting (80,81) and one at the 2000 ASCO meeting (82). Summary data and the previously reported randomized studies are presented in Table 8.

The first study presented at the 1999 ASCO meeting, known as the "Philadelphia" trial (80), enrolled 553 patients but finally randomized only 184 patients: 101 to HDC and 83 to SDC, which actually consisted of 2 years of continuous chemotherapy. The study demonstrated no difference in the EFS or OS for the patients, and all outcome parameters were poor for both arms. It is important to note that further evaluation of the data have shown that the HDC group had significantly more patients with adverse prognostic factors, including prior adjuvant therapy, than the SDC group. The conversion of patients from partial remission after induction therapy to CR after HDC was much lower than had ever been reported previously. The power of the study was further compromised by the inclusion of significant numbers of protocol deviations in the intent-to-treat analysis. The results that have been obtained in PBT-1 are poor compared with almost any other study in metastatic breast cancer that has been reported in the literature. The study also has several other methodological and conduct limitations.

The second randomized clinical trial presented was from France, the Pegase 04 study (81). After initial response of metastatic breast cancer to induction chemotherapy, patients were randomized to receive either HDC or two to four additional cycles of SDC. Time to progression was nearly double for patients receiving intensive therapy (36 months vs 18 months). Similar results were seen in the OS with a median of 18 months on the SDC arm and 36 months on the high-dose arm. Despite the small sample size, the data approached statistical significance ($P = 0.06$).

An overview analysis of trials in metastatic breast

Table 8. Randomized studies in metastatic breast cancer.

PI: Study (HDC regimen)	Patient numbers	Median follow-up, years	Results of study at presentation
Peters: AFM Randomized Study (STAMP1) (77, 78)	425	7	Significant improvement in EFS for CR patients transplanted immediately; delayed HDC provided better OS for CR patients; 12% TRM
Bezwoda: South African Study (CNV) (79)	90	5	Significant improvement in DFS and OS; direct comparison of HDC to SDC. In light of allegations of scientific misconduct in the high-risk primary study, this investigation is also slated for audit
Stadtmauer: PBT-1 (STAMP V) (80)	553/184	3	More than 60% drop-out; overall CR rate, 13%; no difference in DFS or OS; 9-month TTF; no TRM
Lotz: Pegase O4 (CMA) (81)	61	5	Double median DFS; $P = 0.06$; DFS and OS curves come together at 5 years
Madan: AFM Bone Only Study (STAMP I) (82)	85	5	25% of the HDC arm are progression free, whereas all SDC patients had progressed within 2 years

^a PI, principal investigator; CNV, cyclophosphamide-mitoxantrone-VP16; TTF, time-to-treatment failure; CMA, cyclophosphamide-mitoxantrone-melphalan.

cancer using a metaanalysis technique was performed by Dr. Karen Antman and the statistical group from Columbia University Biostatistical Center on the available randomized data in metastatic disease. This demonstrated that HDC produces a statistically significant improvement ($P = 0.049$; presented in discussion at ASCO99).

At the recent 2000 ASCO meeting, data were presented from the Duke group from a phase III study in which patients with bone predominant breast cancer were randomized after four cycles of AFM induction chemotherapy to receive either a STAMP I-based transplant or to be observed (82). All patients randomized to the observation had progressed within 2 years, whereas 25% of those randomized to HDC were without progression with follow-up out to close to 5 years.

Overall, in high-risk primary disease available data suggest that HDC, particularly the non-STAMP V regimens, may have an important role to play, but also that further evaluation is imperative. In metastatic disease, all of the randomized trials must be considered, and when this is done, as analyzed by Antman and colleagues, the overall result indicates a significant advantage in favor of the use of HDC. Only the STAMP V-based study, which appears to have considerable limitations, has been negative. Again, further study is required to define which of the patients with metastatic disease will most benefit.

HDC alone will not completely solve the problem of breast cancer, but it is an active platform on which to build an overall therapeutic strategy. Novel therapeutic advances, including stem cell purging, antibodies, vaccines, immune cellular therapy, angiogenesis inhibitors, and new chemotherapy, must all be evaluated as part of the total strategy.

Conclusion

AHSCT has appropriately moved from the realm of pilot and small phase II studies to larger randomized phase III studies. The modality shows high degrees of activity and has translated into outcomes benefit in several disease settings, but most importantly, it requires ongoing careful

scientific study and refinement to make it safer, to maximize therapeutic benefit by building on current observations, and to define the patients most likely to benefit from the approach.

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